## REMARKS

Claims 118-183 are presently pending in the application and stand rejected under 35 U.S.C. § 112, first paragraph (enablement) and under the judicially created doctrine of obviousness-type double patenting.

**35 U.S.C. § 112, first paragraph**

Applicants acknowledge with appreciation that the rejection of claims 118-183 as allegedly non-enabled for methods of using a zinc finger protein with two or more regulatory domains has been withdrawn in view of the arguments presented in the response and declaration by Adreas Reik, filed 12 February 2003. (Final Office Action, paragraph 1).

The rejection of claims 118-183 as allegedly not enabled for methods in which a ZFP polypeptide is introduced has been maintained. (Final Office Action, paragraphs 3 and 4). The arguments and declaratory evidence filed February 6, 2003 was deemed unpersuasive. (Final Office Action, paragraph 4). In other words, the Office appears to be requiring that data be submitted.

Applicants reiterate that the test of enablement remains whether Applicants' specification (in view of information known in the art) teaches one of skill in the art how to make and use the invention as claimed. In other words, neither data nor working examples are **ever** required in order to show enablement. MPEP 2164.02. Therefore, for the reasons previously of record, Applicants again submit that based on the teachings of the specification and the state of the art at the time of filing, it would not have required undue experimentation for one skilled in the art to identify protein delivery vehicles and use one or more of these vehicles to deliver functional engineered zinc finger proteins to a cell. (See, also Pabo Declaration, paragraphs 5-9).

Nonetheless, Applicants submit herewith still further evidence that the specification as filed fully enables methods in which the ZFP is administered as a polypeptide. In particular, Yeh et al. (2003) *Molecular Therapy* 7(5):S461 Abstract #1191 (Exhibit A), conclusively establishes that peptide-mediated delivery of an engineered ZFP can modulate expression of cellular genes. Indeed, both the VEGF-specific ZFPs and peptide delivery means described in Yeh et al. are clearly set forth in the specifications filed. (see, e.g., Example 1 detailing exemplary VEGF-specific ZFPs and page 44, particularly lines 7-25, detailing the use of membrane translocation peptides (*e.g.,* internalization sequences). Thus, when properly considered, the evidence and facts of record clearly establish that the claims are fully enabled by the specification.

**35 U.S.C. § 103(a)**

Applicants note with appreciation that all the rejections under 35 U.S.C. § 103(a) have been withdrawn. In paragraph 5 of the Final Office Action, it is stated that ". . . one of skill in the art would expect the unmodified exogenous zinc finger proteins of Liu '96 to operate by regulation of gene transcription because at the time of filing of the instant application the prior art, for example Choo *et al.* and Liu *et al.* '97, provided clear teachings that zinc finger proteins acted by modulation of gene transcription."

Applicants disagree with this statement for the reasons of record. In particular, Applicants note that the pending claims recite contacting an engineered zinc finger protein with a target site in an endogenous cellular gene. As pointed out by Dr. Case at the personal interview in parent application 09/229,037 on August 29, 2002, the presence of a binding site for a binding protein within a particular nucleotide sequence does not ensure that the binding protein will bind to that site in a gene; *i.e.*, when the nucleotide sequence comprising the binding site exists within the context of cellular chromatin. Thus, the teaching of an EGR-1 binding site in the TGF-$\beta$1 gene sequence by Liu '96 is not a teaching of the binding of EGR-1 to an endogenous cellular gene.

For these reasons, Applicants respectfully maintain that Liu et al. '96 neither teaches nor suggests a zinc finger protein contacting a target site in an endogenous cellular gene (as claimed), let alone an engineered zinc finger protein contacting a target site in a gene.

The Final Office Action also contains the following statement:

> The argument that the prior art did not show regulation of endogenous genes by engineered zinc finger proteins is persuasive because, as pointed out by the applicants in their response, the prior art such as Choo et al. and Liu et al. '97 showed use of reporter constructs as substrates for engineered zinc finger proteins. The use of reporter constructs in the prior art served to teach away from the use of endogenous genes as targets of action of engineered zinc finger proteins. The cited prior art does not provide motivation to use an endogenous gene as a target of action of an engineered zinc finger protein with a reasonable expectation of success.

Applicants wish to clarify that, in their response, it was stated that the references disclose regulation of several types of non-endogenous genes, of which a reporter gene is but one type. For example, Choo *et al.* discloses regulation of a chromosomally integrated heterologous cDNA comprising portions of two different genes. *See*, for example, Applicants' Response dated February 4, 2003 at pages 5 and 6.

**Obviousness-Type Double Patenting**

The Office again asserts that double patenting exists as between certain of the instant claims and those of copending applications 09/229,037; 09/478,681; and 09/897,844. (Final Office Action, paragraphs 11-13).

With respect to U.S. Serial No. 09/229,037 (now U.S. Patent No. 6,534,261) and U.S. Serial No. 09/478,681 (issue fee paid on April 15, 2003), Applicants will file the appropriate terminal disclaimers upon indication of allowable claims in the pending case. With regard to the provisional rejection over U.S. Serial No. 09/897,844, Applicants will address non-provisional rejections in that case.

## CONCLUSION

Applicants believe that the claimed subject matter is fully enabled in light of the teachings of the specification, and evidence of record (including declaration evidence as well as the attached Abstract). If any issues remain to be addressed, the Examiner is encouraged to telephone the undersigned at (650) 493-3400.

Respectfully submitted,

Date: June 12, 2003

By: _____

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